PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 March 2001 (15.03.01)	
International application No. PCT/GB00/02465	**Applicant's or agent's file reference** 102325/JND
International filing date (day/month/year) 27 June 2000 (27.06.00)	**Priority date** (day/month/year) 28 June 1999 (28.06.99)
Applicant NEW, Roger et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 January 2001 (25.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US)

PCT/GB00/02465

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DANIELS, Jeffrey, Nicholas
Page White & Farrer
54 Doughty Street
London WC1N 2LS
ROYAUME-UNI

Date of mailing (day/month/year)
27 December 2001 (27.12.01)

Applicant's or agent's file reference
102325/JND

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02465

International filing date (day/month/year)
27 June 2000 (27.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

PROXIMA CONCEPTS LIMITED
P.O. Box 29757
London NW3 6ZW
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [X] the nationality [X] the residence

Name and Address

PROXIMA CONCEPTS LIMITED
PO Box 3162
Woodbourne Hall
Road Town
Tortola
Virgin Islands, British

State of Nationality: **
State of Residence: **
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Agnes WITTMANN-REGIS

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004562223

Copy for the Elected Office (EO/US) PCT/GB00/02465

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

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27 December 2001 (27.12.01)

Applicant's or agent's file reference
102325/JND

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02465

International filing date (day/month/year)
27 June 2000 (27.06.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

MOZAIC DISCOVERY LIMITED
PO Box 3162
Woodbourne Hall
Road Town
Tortola
British Virgin Islands

State of Nationality: **
State of Residence: **

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person identified in Box 2 has been added as new applicant for all States except the United States of America.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Agnes WITTMANN-REGIS

Telephone No.: (41-22) 338.83.38

F. ENT COOPERATION TREA.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DANIELS, Jeffrey, Nicholas
Page White & Farrer
54 Doughty Street
London WC1N 2LS
ROYAUME-UNI

Date of mailing (day/month/year)
15 March 2001 (15.03.01)

Applicant's or agent's file reference
102325/JND

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02465

International filing date (day/month/year)
27 June 2000 (27.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
PROVALIS UK LIMITED
Newtech Square
Deeside Industrial Park
Deeside
Flintshire CH5 2NT
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
PROXIMA CONCEPTS LIMITED
P.O. Box 29757
London NW3 6ZW
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Pascal Piriou
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

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PCT/GB00/02465

International filing date (day/month/year)
27 June 2000 (27.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
PROVALIS UK LIMITED
Newtech Square
Deeside Industrial Park
Deeside
Flintshire CH5 2NT
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
PROXIMA CONCEPTS LIMITED
P.O. Box 29757
London NW3 6ZW
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Pascal Piriou

Telephone No.: (41-22) 338.83.38

10/019052
JC Rec'd PCT/PTO 27 DEC 2001

102325/JND/RD/kl

17 December 2001

BY FAX & POST

URGENT REPLY REQUESTED

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20
Switzerland

Dear Sirs,

International Patent Application No. PCT/GB00/02465
Proxima Concepts Limited

We file herewith a Power of Attorney signed on behalf of the present applicant for the above International application, Proxima Concepts Limited. We also enclose copies of the Powers of Attorney signed by Istvan Toth, Roger New and Provalis UK Limited which were filed at the UK Patent Office on 4 October 2000.

We wish to record a change in the details of the present applicant. The new details for Proxima Concepts Limited are:

PO Box 3162
Woodbourne Hall
Road Town
Tortola
British Virgin Islands

Proxima Concepts Limited is a company incorporated in the British Virgin Islands.

We also wish to add a further applicant for all designated states except the United States of America. The name and address of the new co-applicant is:

Mozaic Discovery Limited
PO Box 3162
Woodbourne Hall
Road Town
Tortola

British Virgin Islands

Mozaic Discovery Limited is a company incorporated in the British Virgin Islands.

Accordingly, the co-applicants for all designated states except the United States of America are now Proxima Concepts Limited and Mozaic Discovery Limited.

We urgently require a notification confirming that the International Bureau has recorded this change, in order that we can proceed to enter the initial phase in various territories with the correct names and addresses of the applicants listed. The due date of entry to the national phase expires on 28 December 2001. Accordingly, please send us the notification **BY FAX** as soon as possible. We would greatly appreciate receiving the notification by 20 December 2001 at the very latest.

Thank you for your help in this matter.

Yours faithfully,

Jeffrey Nicholas Daniels
(Authorised Representative)

Enc.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 102325/JND

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB00/02465	27 June 2000	28 June 1999

Title of invention: Epitopes Formed by Non-Covalent Association of Conjugates

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Proxima Concepts Limited
P O Box 29757
London NW3 6ZW

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: United Kingdom (GB)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NEW, Roger
Flat 10
Leinster Mansions
No 1 Langland Gardens
London NW3 6QB

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: United Kingdom (GB)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TOTH, Istvan
5 Zelita Road
Moggill
Queensland 4070
Australia

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: Australia (AU)

☐ Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No.
PCT/GB00/02465

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [x] agent [ ] common representative

and [x] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DANIELS, Jeffrey Nicholas (GB)
PAGE WHITE & FARRER
54 Doughty Street
London WC1N 2LS
United Kingdom

Telephone No.: 020 7831-7929

Facsimile No.: 020 7831-8040

Teleprinter No.: 8955681

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[ ] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[x] which is the language in which the international application was filed.

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 3

International application No.
PCT/GB00/02465

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:		sheets	☐	☐
2. amendments under Article 34	:		sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:	1	sheets	☐	☐
6. other *(specify)*	:		sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [x] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....
JEFFREY NICHOLAS DANIELS
Authorised Representative

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. [ ] The applicant has been informed accordingly.
4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. [ ] Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 102325/JND

Box No. I TITLE OF INVENTION

LIGAND-BINDING COMPOSITION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PROVALIS UK LIMITED
Newtech Square
Deeside Industrial Park
Deeside
Flintshire CH5 2NT
United Kingdom

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: United Kingdom (GB)

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NEW Roger
Flat 10
Leinster Mansions
No 1 Langland Gardens
London NW3 6QB
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: United Kingdom (GB)

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DANIELS, Jeffrey Nicholas
Page White & Farrer
54 Doughty Street
London WC1N 2LS
United Kingdom

Telephone No.
020-7831-7929

Facsimile No.
020-7831-8040

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TOTH Istvan
5 Zelita Road
Moggill, Queensland 4070
Australia

This person is:

- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: United Kingdom (GB)

State *(that is, country)* of residence: Australia (AU)

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania
☒ **AM** Armenia
☒ **AT** Austria
☒ **AU** Australia
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina
☒ **BB** Barbados
☒ **BG** Bulgaria
☒ **BR** Brazil
☒ **BY** Belarus
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China
☒ **CR** Costa Rica
☒ **CU** Cuba
☒ **CZ** Czech Republic
☒ **DE** Germany
☒ **DK** Denmark
☒ **DM** Dominica
☒ **EE** Estonia
☒ **ES** Spain
☒ **FI** Finland
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia
☒ **GH** Ghana
☒ **GM** Gambia
☒ **HR** Croatia
☒ **HU** Hungary
☒ **ID** Indonesia
☒ **IL** Israel
☒ **IN** India
☒ **IS** Iceland
☒ **JP** Japan
☒ **KE** Kenya
☒ **KG** Kyrgyzstan
☒ **KP** Democratic People's Republic of Korea
☒ **KR** Republic of Korea
☒ **KZ** Kazakhstan
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco
☒ **MD** Republic of Moldova
☒ **MG** Madagascar
☒ **MK** The former Yugoslav Republic of Macedonia
☒ **MN** Mongolia
☒ **MW** Malawi
☒ **MX** Mexico
☒ **NO** Norway
☒ **NZ** New Zealand
☒ **PL** Poland
☒ **PT** Portugal
☒ **RO** Romania
☒ **RU** Russian Federation
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia
☒ **SK** Slovakia
☒ **SL** Sierra Leone
☒ **TJ** Tajikistan
☒ **TM** Turkmenistan
☒ **TR** Turkey
☒ **TT** Trinidad and Tobago
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine
☒ **UG** Uganda
☒ **US** United States of America
☒ **UZ** Uzbekistan
☒ **VN** Viet Nam
☒ **YU** Yugoslavia
☒ **ZA** South Africa
☒ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ People's Democractic Republic of Algeria
☒ Antigua and Barbuda
X Republic of Mozambique

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is ***insufficient*** *to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

(i) ***if more than two persons are involved as applicants and/or inventors*** *and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication ***"the States indicated in the Supplemental Box"*** *is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, ***the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America****: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are ***further agents****: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "****patent of addition****," or "****certificate of addition****," or if, in Box No. V, the name of the United States of America is accompanied by an indication "****continuation****" or "****continuation-in-part****": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) if, in Box No. VI, there are ***more than three earlier applications whose priority is claimed****: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

(vii) if, in Box No. VI, ***the earlier application is an ARIPO application****: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.*

2. If, with regard to the ***precautionary designation statement*** *contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning ***non-prejudicial disclosures or exceptions to lack of novelty****: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

PALMER, Roger (GB)
RICHARDS, David John (GB)
JENKINS, Peter David (GB)
DRIVER, Virginia Rozanne (GB)
STYLE, Kelda Camilla Karen (GB)
SHACKLETON, Nicola (GB)
SLINGSBY, Philip Roy (GB)
NEOBARD, William John (GB)
HILL, Christopher Michael (GB)
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PATENT COOPERATION TREATY

REC'D 31 JUL 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
102325/JND		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02465	27/06/2000	28/06/1999
International Patent Classification (IPC) or national classification and IPC G01N33/543		
Applicant PROXIMA CONCEPTS LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/01/2001	27.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Knudsen, H Telephone No. +49 89 2399 8696

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02465

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-26 as originally filed

Claims, No.:

1-31 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-31
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

CITED PRIOR ART DOCUMENTS:

D1: US-A-5,882,645 discloses a compound in which amino acids form a peptide part and a lipophilic moiety forms a lipophilic anchor. The lipophilic moiety may be anchored in a liposome. Different peptide antigens may be kept together by covalent binding via lysine residues.

D2: EP-A-0 338 437 disclose a vaccine against mouth and foot disease which employs a mixture of synthetic peptide sequences bonded to lipophilic anchor(s).

D3: US-A-5 580 563 discloses a multiple antigen system in which a number of peptide antigens are bonded covalently via trivalent lysine residues and via a peptide spacer are attached to a lipophilic anchor. The compositions may employ a mixture of lipophilic substances.

NOVELTY:

5.1 The only prior art document which discloses a composition containing a plurality of conjugates of head and tail groups is D2. In D1 and D3 the different peptide antigens are covalently attached to each other. The vaccine of D2, however, discloses peptide antigens which are bonded to separate antigen recognition sites and give rise to different antibody. There is no reason to expect that the antigens show synergy in presenting the individual antigenic epitopes. Thus, the feature that the head groups are positioned to form an epitope capable of interacting with the ligand more strongly than each of the head groups individually is not disclosed in D2 and claim 1 is therefore considered novel. Dependent claims 2-12 and the methods for producing the composition (claims 13-31) are considered novel for the same reasons.

INVENTIVE STEP:

5.2 According to the description (p.1-2, bridging paragraph), the present invention solves the problem of providing a receptor-specific therapeutic strategy without

the need of employing large proteins. None of the cited prior art documents suggest the use of a composition containing non-covalently associated conjugates with head and tail in which two head groups are required for presenting the epitope to the ligand. Claims 1-31 are therefore considered inventive (see however Item VIII).

INDUSTRIAL APPLICABILITY:

5.3 Claims 1-31 appear to be industrially applicable.

Re Item VII

Certain defects in the international application

7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1-D3 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

Re Item VIII

Certain observations on the international application

8.1 It follows from the wording of claim 1 that the in-vivo use of non-covalently associated conjugates will only be effective in case the head groups are closely associated when presented to the ligand. As stated in the application's description (p.20) it is important for this purpose that all of the conjugates are presented in combination on the same supramolecular assembly. There is nothing in the application which suggests that the claimed compositions, which are not so associated, have any effect in therapy. Claims 1-10, 12-24 and 26-31 which do not mention a supramolecular association are therefore considered to lack an essential feature of the invention.

8.2 The definition of the invention in the claims is based on a restatement of the goal to be achieved, namely that the head groups are in association to form an epitope capable of interacting with the ligand more strongly than each of the head groups individually, but none of the claims mention the technical features essential to obtaining this effect. The claims are therefore not defined by the technical features of the invention and therefore lack clarity.

8.3 Moreover, the claims lack clarity because their content is defined partly by the properties of an undefined ligand. It is impossible for the skilled person to determine on the basis of this wording whether a composition falls within the scope of the claims, because he/she would have to test the composition against an indefinite number of ligands in order to establish whether or not the composition showed the required binding properties with a ligand and therefore fall within the scope of the claims.

8.4 The claims lacks support in the description for the further reason that none of the examples illustrate one way of carrying out the invention. In detail the following deficiencies were observed in the examples:

8.4.1 None of the examples disclose an assay which can be used as a model for a pharmacologically important ligand-epitope interaction.

Examples 1-3 describe methods in which an expression product from a cell or the oral uptake of radiolabelled peptide-lipid conjugates in mice are determined. Neither of these methods are therefore specific for a ligand- epitope interaction and therefore cannot be used in the demonstration of the efficiency of the claimed compositions.

Example 4 shows that some combinations bind to goat IgG more efficiently than other combinations. However, this assay does not appear to take account of the different hydrophobicity of the combinations which may cause binding to the solid phase to a different extent and does not show whether the combinations bind to a larger extent than the binding of the single components added together.

8.4.2 The nature of the lipid used in examples 1 and 3-4 is not specified and in Example 2 it is not described how the peptides are associated with the phosphatidyl choline or octyl glucoside.

8.5 The application is described on the basis of amino acids as head groups, insofar as the claims encompass other moieties this is not supported at all by the description.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
102325/JND		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02465	27/06/2000	28/06/1999
Applicant		
PROVALIS UK LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

EPITOPES FORMED BY NON-COVALENT ASSOCIATION OF CONJUGATES

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 00/02465

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/543 G01N33/50 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 882 645 A (GIBBONS WILLIAM ANTHONY ET AL) 16 March 1999 (1999-03-16) figures 1-3	1-31
A	EP 0 338 437 A (HOECHST AG) 25 October 1989 (1989-10-25) page 5, line 48 - line 50; claims 1,7,8	1-31
A	US 5 580 563 A (TAM JAMES P) 3 December 1996 (1996-12-03) column 8 -column 9; figure 1; example 1	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2000	27/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hart-Davis, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted] 00/02465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5882645 A	16-03-1999	AU 4715493 A	14-02-1994
		DE 69315842 D	29-01-1998
		DE 69315842 T	09-04-1998
		EP 0652896 A	17-05-1995
		ES 2111167 T	01-03-1998
		WO 9402506 A	03-02-1994
EP 0338437 A	25-10-1989	DE 3813821 A	02-11-1989
		AT 118507 T	15-03-1995
		AU 619826 B	06-02-1992
		AU 3326589 A	26-10-1989
		CA 1333563 A	20-12-1994
		DE 58908990 D	23-03-1995
		DK 192889 A	23-10-1989
		ES 2068215 T	16-04-1995
		GR 3015358 T	30-06-1995
		IE 67124 B	06-03-1996
		JP 2006410 A	10-01-1990
		JP 2837866 B	16-12-1998
		NZ 228824 A	26-05-1992
		PT 90333 A,B	10-11-1989
		SU 1836102 A	23-08-1993
		US 6074650 A	13-06-2000
		US 6024964 A	15-02-2000
		ZA 8902954 A	27-12-1989
US 5580563 A	03-12-1996	WO 9322343 A	11-11-1993

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

EPITOPES FORMED BY NON-COVALENT ASSOCIATION OF CONJUGATES

The present invention relates to a composition for interacting with a ligand, a method for producing such a composition and a method for producing a molecule based on the composition.

Background of the Invention

Protein receptors are known normally to bind to their target ligands via epitopes, which constitute a small proportion of the total protein molecule. For maximum binding or interaction, the structure of the epitope needs to be maintained in a rigid conformation in order to form a binding site containing all the necessary components of the epitope in close proximity. Attempts to produce an analogous peptide constructed solely of the amino acids comprising the binding site often fail because these peptides do not possess the same biological activity as the protein receptor. This is attributed to the peptide having a different conformation in free solution from that of the entire protein receptor. In addition, where the binding site of a protein is constructed of oligo-peptides from different, non-contiguous parts of a protein chain, mixing isolated oligopeptides in free solution does not result in reconstitution of the active binding site.

Being constrained to use such large proteins to present binding-site epitopes gives rise to several problems in development of new receptor-specific therapeutic strategies. One problem is that such large proteins can readily evoke an

immune response. A second problem is that long peptide chains are susceptible to attack by endopeptidases, such as those in the lumen of the gut. Finally, these large proteins can be costly to manufacture, purify and maintain in stable form.

Summary of the Invention

The present invention aims to overcome the disadvantages of the prior art.

In a first aspect, the invention provides a composition for interacting with a ligand, which composition comprises a non-covalent assembly of a plurality of distinct conjugates, each conjugate comprising a head group and a tail group, wherein the tail groups of the conjugates form a hydrophobic aggregation and the conjugates have freedom of motion with respect to each other within the assembly so that, in the presence of a ligand, at least two of the head groups (which are the same or different) are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually. The head groups are typically hydrophilic and the tail groups typically hydrophobic, eg lipophilic, composed of hydrocarbon chains, halophilic, constructed of fluorocarbon chains, or silane based.

By constructing conjugates with a head group and a tail group in accordance with the present invention, the tail groups can associate to form a hydrophobic aggregation which is typically a supramolecular assembly such as a micelle, a

lamellar structure, a liposome or other lipid structure, in which the conjugate are oriented whereby the head groups are brought into close proximity when in an aqueous phase. Because the conjugates are movable within the assembly, the head groups are able to adopt a number of different positions within the assembly. The head groups, which are typically non-identical, are therefore free to move within the assembly and, surprisingly, to interact cooperatively to induce biological consequences which the head groups on their own are not capable of eliciting. A further unexpected finding is that assemblies composed of combinations of different headgroups are capable of eliciting biological responses or participating in binding with biological receptors while assemblies composed of single headgroups are not capable of acting in this way.

As indicated above, these supra-molecular assemblies are typically particulate or colloidal in nature, usually comprising many hundreds of sub-units (the conjugates) all oriented with the headgroups directed outwards from the centre of the particle as shown in Figure 1a. Each of the conjugates may change its location within the assembly, being free to exchange places with adjacent conjugates by a process of Brownian motion and, in so doing, may migrate over the whole surface of the assembly. Other manifestations of supra-molecular assemblies are cubic phases and coated surfaces.

Each conjugate in the assembly may have a head group selected from one chemical or biological class or a number of

different classes, such as an amino acid or peptide; a peptide analogue; a mono-, di- or poly-saccharide; a mono-, di- or poly-nucleotide; a sterol; an alkaloid; an isoprenoid; an inositol derivative; a single or fused aromatic nucleus; a water-soluble vitamin; a porphyrin or haem nucleus; a phthalocyanine; a metal ion chelate; a water-soluble drug; a hormone; or an enzyme substrate.

In one preferred embodiment, each head group comprises an amino acid or oligo-peptide, which may be the terminal portion of a peptide chain. It is desirable to keep the length of the peptide to a minimum so as to avoid eliciting an immune response where the composition is to be used *in vivo*. Accordingly, it is preferred that the peptide is no more than six amino acids long.

The amino acids employed can be any of the natural amino acids, substituted derivatives, analogues, and D- forms thereof.

The tail groups of the conjugates may be all the same or may be a mixture of different tail groups, each of which preferably comprises a hydrophobic group selected from a linear, branched, cyclic, polycyclic, saturated or unsaturated construct, with or without hetero-atoms included in the structure which can be substituted or unsubstituted, for example, a lipidic amino acid analogue; a prostaglandin; a leukotriene; a mono- or diglyceride; a sterol; a sphingosine or ceramide derivative; and a silicon or halogen-substituted derivative of such a hydrophobic group. The tail group preferably has from 6 to 24 carbon atoms and more

preferably comprises from 10 to 14 carbon atoms. More than one tail group may be present in each conjugate. For example, one or more lipidic amino acids with hydrocarbon side chains may form part of each conjugate, linked to one or more amino acids in the head group.

Any chemical method may be used to link the head group to the tail group. For example, each conjugate may further comprise a spacer group linking the head group to the tail group so as to facilitate presentation of the head group on the surface of the non-covalent association. Such spacer groups are well known and include, for example, amino acids, hydroxy acids, sugars and polyethylene glycol.

In a further aspect, the present invention provides a composition as defined above, for use as a medicament, a prophylactic or a diagnostic.

An advantage of the invention is that strong specific binding interactions can be achieved with conjugates in which the head groups are small in comparison to conventional biological receptors. If the head group is an oligo-peptide, for example, then the length of the peptide chain would not normally exceed ten amino acids and would preferably be six or less. Accordingly, compositions according to the present invention can be made far less immunogenic than their protein counterparts.

In accordance with this aspect of the invention, not only can the composition of the present invention be formulated to

interact with a ligand *in vitro* but also the composition can be used *in vivo*, optionally formulated with a suitable diluent, excipient or carrier in accordance with a suitable delivery route.

In a further aspect, the present invention provides use of a conjugate comprising a head group and tail group for the preparation of the composition as defined above.

There is further provided a method for producing a composition for interacting with a ligand, which method comprises:
(a) providing a plurality of distinct conjugates, each conjugate comprising a head group and a tail group; and (b) forming from the plurality of conjugates, by noncovalent association thereof, an assembly in which the tail groups aggregate hydrophobically and in which the conjugates exhibit freedom of motion relative to one another so that, in the presence of a ligand, at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually. Each conjugate is preferably as defined above.

The conjugates may be dispersed in aqueous phase by a variety of known methodologies for the preparation of lipid vesicles, including mechanical mixing, exposure to high shear forces, sonication, solvent dispersion or codissolution with detergents. Typically, the non-covalent supra-molecular assemblies formed thereby will be composed of several

different conjugates mixed together. Additional lipidic materials may optionally be added to alter surface properties, to aid in the dispersion of the conjugates, to stabilise the non-covalently associated assembly of conjugates, to aid in the presentation of head groups of the conjugates, or to permit the construction of vehicles which can be targeted by the epitopes formed upon random movement of the conjugates and appropriate positioning of the head groups within the assembly.

An important aspect of the method according to the present invention involves the step of identifying the plurality of conjugates which has the desired biolgical activity. In a preferred aspect, this step comprises

(i) selecting a set of conjugates with an array of head groups;

(ii) forming a non-covalent association therefrom, in which.the tail groups aggregate hydrophobically and in which the conjugates exhibit freedom of motion with respect to one another;

(iii) assaying for sufficient interaction between the non-covalent association and the ligand;

(iv) optionally repeating steps (i) to (iii) using a set of conjugates with a modified array of head groups; and

(v) on finding sufficient interaction in step (iii), selecting the set of conjugates as the plurality of conjugates in step (a).

Examples of assays for "sufficient interaction" may include binding assays such as those utilising the ELISA principle for detection of association between antibody and antigen. Other suitable *in vitro* assays include modification of fluorescence of environmentally-sensitive membrane-bound fluorescent probes, precipitation reactions, enhancement or inhibition of enzyme activity etc. Assays relying on the abilty of materials to alter the behaviour of cells cultured *in vitro* may also be appropriate, such as assays for cell death, cell proliferation, apoptosis, inhibition or stimulation of cell-to-cell contact, secretion of cytokines or other soluble products, synthesis of specific m-RNA, intracellular vesicular transport, alteration of cell signalling processes etc. *In vivo* assays in whole animals or humans may also be carried out, for example incorporation of radiolabel into the supramolecular assemblies, followed by investigation of its subsequent distribution after administration by various routes.

According to this method a combinatorial approach is used in which a range of different supra-molecular assemblies (or "probes") is prepared, each containing a different combination of conjugates selected from a pre-synthesised bank. Selection of the appropriate conjugates may be based on known properties of the target ligand or may simply involve the use of a very wide range of head groups to

increase the probability that two or more of the head groups will form an epitope for the ligand. In this way, following the assay for sufficient interaction between the probe and the ligand as described above, the combination of conjugates found to be most effective may be modified by adding further head groups, removing some head groups, or both, and assaying the resultant probes once again for sufficient interaction. Eventually, the most favourable combination of head groups may be identified and selected for use in the composition.

The present invention therefore has a very clear advantage over traditional combinatorial chemistry. In combinatorial chemistry, the identification of the most favourable sequence for binding to a specific receptor must be carried out by synthesis of hundreds of possible combinations of different groups such as amino acids, in different orders, each one having to be tested for efficacy. This process is time-consuming, expensive and is limited by the nature of the chemistry which can be carried out in linking the different components together. In contrast, the present invention simply relies upon proximity of the head groups to provide association-derived epitopes. Once a set of conjugates has been synthesised, no further synthetic chemistry is required, only simple mixing of the conjugates to form the different probes by non-covalent association.

In a preferred simple embodiment, the present method uses conjugates having a single terminal amino acid linked via a spacer to a lipid tail group which can be combined simply by mixing in aqueous medium to form micelles in which different

amino acid side chains would be presented together in a multiplicity of different configurations. Accordingly, the need to present amino acids in a specific order, or with a specific spacing or orientation, is circumvented. On statistical grounds, a proportion of the individual amino acid sub-units will always be associated in an ideal configuration.

In one arrangement, each of the conjugates would have the linear structure: X-spacer-spacer-lipid-lipid, where X represents a single amino acid different for each of the distinct conjugates employed.

When seeking to construct epitopes composed of natural amino acids it is possible to simplify further the number of head groups for selection. One can categorise the amino acid residues found in natural proteinaceous materials into six fundamental classes preferably using in any one class one amino acid rather than all members of that class because of the increased spatial flexibility of amino acids in the terminal position of the head group. This has the effect of reducing considerably the total number of amino acids required for constructing the pre-synthesised bank of conjugates and thereby the total number of head groups used. The main classes of amino acids are set out in Table 1 below.

Table 1

Class	**Representative Abbreviation**

Hydrophobic	Leucine	L
Hydroxylic	Serine	S
Acidic	Glutamate	E
Amide	Glutamine	Q
Basic	Histidine	H
Aromatic	Tyrosine	Y

A number of strategies are available for identifying active combinations of amino acid-containing conjugates.

In one embodiment, a restricted number of conjugates is employed to form a range of distinct probes where each probe is an aqueous suspension of supra-molecular assemblies, each assembly consisting of selected conjugates mixed together, and each differing from the other as a result of the inclusion of a different additional conjugate as shown below where each of the letters given represents a conjugate with a different terminal amino acid:

Probe 1 A B C D
Probe 2 A B C E
Probe 3 A B C F
Probe 3 A B C G
.....
.....
Probe x A B C Z

Each of the probes is tested separately in the biological assays for sufficient binding as outlined above.

In a second simple embodiment, an initial probe can be constructed which contains a large number of different conjugates from the bank, and its efficacy compared with probes each lacking a different conjugate in turn, to determine which headgroups in the bank are essential, and which are redundant for the biological interaction being investigated. This approach is illustrated below:

Probe 1 A B C D E . . . Z
Probe 2 A C D E . . . Z
Probe 3 A B D E . . . Z
.....
Probe x A B C D E . . .

Combinations of the alternative approaches as outlined above can be made.

A knowledge of the target ligand may assist in designing a suitable starting array. For example, if the ligand is known to be basic, it would make sense to impart an acidic character to the conjugates by presenting them in the form where a free carboxyl group of the terminal amino acid is exposed. Introducing additional functionality by employing a particular amino acid as a spacer group adjacent to the terminal amino acid may also confer increased specificity. Where the involvement of, say. a short oligo-peptide sequence of known structure has already been implicated in binding to the target ligand, such a sequence may be incorporated into a conjugate to be included in the set of conjugates making up the composition.

In a final aspect, the present invention provides a method for producing a molecule for interacting with a ligand. The method comprises producing a composition according to one of the methods defined above; identifying the at least two head groups which form an epitope for the ligand in the composition; and producing a molecule incorporating the functional groups of the at least two head groups optionally spaced apart by one or more linker groups so that the molecule is capable of interacting with the ligand more strongly than each of the head groups individually.

Whilst the compositions of the present invention may themselves be useful in *in vitro* or *in vivo* systems perhaps to induce a biological response in a therapeutic, prophylactic or diagnostic method, in some circumstances a molecule may be produced based on the structure of the above compositions. By identifying the functional groups of the at least two head groups which form the epitope for the ligand a new molecule analogous to the composition may be produced containing the same or a similar epitope. The functional groups may, for example, be incorporated into a .single linear oligo-peptide possibly with one or more linker groups to space the functional groups apart.

Brief Description of the Drawings

The invention will now be described in further detail, by way of example only, with reference to the following Examples and the attached drawings, in which:

FIGURE 1 shows a schematic representation of the surface of a supra-molecular assembly, and how such a composition according to the present invention binds to a target ligand; and

FIGURE 2 shows a schematic representation of the surface of a supra-molecular assembly composed of two non-identical conjugates whose headgroups consist of short-chain linear peptides.

Detailed Description of the Invention

Referring to Figure 1, a section 1 of a composition according to the present invention is shown in the form of a micelle in which the head groups 2 and tail groups 3 together form conjugates 4 (Fig. 1A). A target ligand 5 is presented to the composition 1. Because the conjugates are movable, a rearrangement occurs (Fig. 1B) to allow positioning of the head groups 2 to bind the target ligand 5. Referring to Figure 2, a section of a composition according to the present invention is shown in the form of a supramolecular assembly, in which binding of a ligand to the surface of the assembly is brought about by the creation of an epitope constructed via the non-covalent association of two conjugates composed of short-chain peptides (A), this epitope being able to interact with the ligand more strongly than either of the individual conjugates in isolation (B). The same principle applies for headgroups containing structures other than amino acids.

EXAMPLES

In the examples given below, the standard convention for representation of amino acids by single letters of the alphabet is employed, except that in all cases the letter refers to conjugates as described above in which that particular amino acid occupies the terminal position in the peptide chain. In the examples described here, the lipid comprises two amino acids linked via a peptide bond, in which both of the amino acids are glycine analogues, where in each case the alpha hydrogen has been replaced by a linear hydrocarbon chain containing either 12 or 14 carbons. Linkages between the headgroup and spacer and the spacer and lipid are all via peptide bonds. The headgroup bears a free amino group and the free end of the lipid bears a $CONH_2$ group. The structure of each conjugate is thus: NH_2-headgroup-spacer-amino acid (C_{14} side chain)-amino acid (C_{12} side chain)-$CONH_2$.

Example 1: Stimulation of TNF secretion from macrophages

1. Individual conjugates E, Y, Q, S & H (linked to lipid via a serine-glycine spacer) were prepared as solutions in methanol/dichloromethane 1:1 at a concentration of 5mg/ml.

2. Solutions of the conjugates were dispensed into 7ml glass vials in equal proportions, to give a final volume of 400ul (2mg of solid) in all vials, as shown in the example overleaf. In cases where the volume of organic solution available was insufficient, adjustment was made at a later stage, when the quantity of water added for reconstitution was reduced accordingly, as shown.

3. The contents of all vials were dried down under a stream of nitrogen, then exposed to a vacuum of at least 1mbar overnight in a lyophiliser.

4. On the following day, distilled water was added in volumes as indicated in the table overleaf, to give a final concentration in all vials of 1mg/ml. The vials were capped, warmed to 37 degC and bath-sonicated until clarity was achieved.

5. The samples were then applied to wells of 24-well cluster plates into which cells of the J774A-1 macrophage cell line had been plated (5 x 10^4cells/ml/well). Volumes of 100ul and 10ul of sample were added to individual wells, and the cells were incubated overnight at 37 degC in an atmosphere of 5% CO_2/air.

6. The following day, duplicate volumes of 50ul of supernate were taken from each well and measured for TNF concentration in a capture ELISA assay. Results obtained are shown in the table below.

	Volume of conjugate dispensed					Volume of water added
	E	Y	Q	S	H	
E	260ul					1.3ml
Y		400ul				2.0ml
Q			310ul			1.55ml
S				360ul		1.8ml
H					400	2.0ml
EY	200ul	200ul				2.0ml
EQ	200ul		200ul			2.0ml
ES	200ul			200ul		2.0ml
EH	200ul				200ul	2.0ml
YQ		200ul	200ul			2.0ml
YS		200ul		200ul		2.0ml
YH		200ul			200ul	2.0ml
QS			200ul	200ul		2.0ml
QH			200ul		200ul	2.0ml
SH				200ul	200ul	2.0ml
QSH			133ul	133ul	133ul	2.0ml
YSH		133ul		133ul	133ul	2.0ml
YQH		133ul	133ul		133ul	2.0ml
YQS		133ul	133ul	133ul		2.0ml
ESH	133ul			133ul	133ul	2.0ml
EQH	133ul		133ul		133ul	2.0ml
EYH	133ul	133ul			133ul	2.0ml
EYS	133ul	133ul		133ul		2.0ml
EYQ	133ul	133ul	133ul			2.0ml
EQS	133ul		133ul	133ul		2.0ml
EYQS	50ul	50ul	50ul	50ul		1.0ml
EYQH	50ul	50ul	50ul		50ul	1.0ml
EYSH	50ul	50ul		50ul	50ul	1.0ml
EQSH	50ul		50ul	50ul	50ul	1.0ml
YQSH		50ul	50ul	50ul	50ul	1.0ml
EYQSH	40ul	40ul	40ul	40ul	40ul	1.0ml

	OD_{450} in J774 supernates		
	100ug	10ug	0ug
E	0.628	0.098	0.013
Y	0.313	0.053	
Q	0.083	0.015	
S	0.348	0.143	
H	0.632	0.206	
EY	0.198	0.027	
EQ	0.113	0.022	
ES	0.211	0.225	
EH	0.167	0.037	
YQ	0.245	0.034	
YS	0.786	0.363	
YH	0.541	0.133	
QS	0.212	0.025	
QH	0.135	0.027	
SH	0.515	0.177	
QSH	0.253	0.032	
YSH	0.712	0.229	
YQH	0.290	0.020	
YQS	0.519	0.119	
ESH	0.380	0.246	
EQH	0.107	0.026	
EYH	0.254	0.042	
EYS	1.289	0.355	
EYQ	0.191	0.064	
EQS	0.209	0.027	
EYQS	0.777	0.206	
EYQH	0.224	0.067	
EYSH	0.262	0.146	
EQSH	0.149	0.185	
YQSH	0.319	0.045	
EYQSH	0.375	0.073	

It can be seen that some, but not all, of the combinations of different headgroups elicit strong biological responses, indicating that the response is specific to those particular combinations. The example illustrates the way in which the conjugates described can be employed in the combinatorial

approach to identify efficacious combinations for the purpose of eliciting a desired biological response.

Example 2: TNF secretion from macrophages

Comparison of supra-molecular assemblies containing a mixture of conjugates, with a mixture of supra-molecular assemblies each containing a single conjugate

Samples were prepared as described in Example 1, with or without the inclusion of additional lipidic materials as described below. The combination of conjugates Y, S and L was chosen since this combination was a good performer in the experiment described in Example 1.

Probes containing phosphatidyl choline were prepared at a ratio of phospholipid to conjugate of 2:1 wt/wt.

Probes containing octyl glucoside were prepared at a ratio of glycolipid to conjugate of 1:1 wt/wt.

Results shown in the table below are optical densities at 450nm of TNF ELISAs conducted on 18 hour culture supernatants. The concentration of conjugate in the wells was 10ug/ml

	OD_{450} of TNF ELISA
EYS	0.390
E+Y+S	0.059
medium control	0.000
EYS:OG	0.559
(E+Y+S):OG	0.193
OG control	0.228
EYS:PC	0.320
(E+Y+S):PC	0.130
PC control	0.081

This example shows that combinations of the conjugates can elicit biological responses either when presented alone, or when presented in conjunction with other lipids, such as phospholipids or lipid sugars. It also shows that for efficacy to be manifested, it is important for all of the conjugates to be presented in combination on the same supra-molecular assembly, and that activity is not observed if the same conjugates are presented together at the same time, but separated on different supra-molecular assemblies. This suggests that it is important to present the conjugates in close proximity to each other, in order to permit the formation of epitopes formed by non-covalent association of the conjugates, which can participate in specific binding with cell-surface receptors.

Example 3: Enhancement of Oral Uptake

1. Individual conjugates L, S, E & Q (conjugated to lipid via a tyrosine-glycine spacer) were prepared as solutions in benzyl alcohol at a concentration of 10mg/ml.

2. 75ul of ^{14}C-cholesterol oleate (3.7MBq/ml in toluene) was dispensed into four 7ml glass screw-capped vials and dried down under a stream of nitrogen.

3. 400ul of each of the solutions in (1) was added to one of the vials in (2) and shaken overnight at room temperature.

4. Solutions of the conjugates were dispensed into 7ml glass vials in equal proportions, to give a final volume of 80ul (0.8mg of solid) in all vials, as shown in the example below.

	L	S	E	Q
L	80ul	-	-	-
S	-	80ul	-	-
E	-	-	80ul	-
Q	-	-	-	80ul
LS	40ul	40ul	-	-
LE	40ul	-	40ul	-
LQ	40ul	-	-	40ul
SE	-	40ul	40ul	-
SQ	-	40ul	-	40ul
EQ	-	-	40ul	40ul
LSE	27ul	27ul	27ul	-
LSQ	27ul	27ul	-	27ul
LEQ	27ul	-	27ul	27ul
SEQ	-	27ul	27ul	27ul
LSEQ	20ul	20ul	20ul	20ul

5. 2ml of distilled water was added to each of the vials with vortexing. The vials were then capped and bath-sonicated for 20 minutes.

6. The samples were then frozen in liquid nitrogen and lyophilised overnight.

7. The following day, each vial was reconstituted with 2ml of distilled water and sonicated again until clear dispersions were achieved.

8. The samples were administered by oral gavage to Balb/c female mice (20-25g weight - four mice per group) at a dose of 0.3ml per animal.

9. 75ul heparinised blood samples were taken by tail venupuncture at 45, 90 and 180 minutes after administration.

10. Each sample was diluted in 0.5ml of PBS, which was then centrifuged, and 0.4ml of the supernate was transferred to a scintillation vial to which 2ml of Optiphase Hisafe 3 (Wallac) was added with mixing.

11. Activity in the samples was measured in a scintillation counter.

Percentage uptake was estimated on the basis of a 2ml blood volume, of which 1ml was assumed to be plasma.

Results are shown in the table below.

	% uptake in bloodstream		
	45mins	90mins	180mins
L	0.90	1.39	0.61
S	1.12	1.14	0.81
E	0.85	1.55	0.79
Q	1.40	3.00	0.81
LS	2.87	2.38	0.66
LE	2.59	2.22	0.49
LQ	5.05	2.15	0.45
SE	4.21	1.66	0.70
SQ	4.67	1.45	0.67
EQ	3.72	2.65	0.59
LSE	1.91	1.20	0.97
LSQ	6.23	1.90	0.80
LEQ	2.77	1.73	0.98
SEQ	3.06	1.52	0.63
LSEQ	2.45	1.74	0.81

It can be seen that some, but not all, of the combinations of different headgroups enhance uptake of label via the oral route, indicating that the response is specific to those particular combinations. The example illustrates the way in which the conjugates described can be employed in the combinatorial approach to identify efficacious combinations capable of acting as targeting ligands.

Example 4: ELISA Fc binding

1. 100ul of goat IgG (1mg/ml) was added to 20ml of PBS and 100ul was placed in each well of a flat-bottomed microtitre plate.

2. The plate was incubated for several days at +4degC.

3. 2mg of each of the conjugates Y, F, W, L, S, E, Q & R (each linked to lipid via a serine-glycine spacer) were weighed into 1ml glass vials and 200ul of benzyl alcohol added to give solutions of each conjugate at a concentration of 10mg/ml.

4. The solutions were dispensed in 7ml glass screw-capped vials as follows:

Vial No.	**Y**	**F**	**W**	**L**	**S**	**E**	**Q**	**R**
1	20ul	20ul	20ul	-				
2	20ul	20ul	-	20ul				
3	20ul	-	20ul	20ul				
4	-	20ul	20ul	20ul				
5					20ul	20ul	20ul	-
6					20ul	20ul	-	20ul
7					20ul	-	20ul	20ul

5. The contents of each vial were mixed well by vortexing, then 1.5ml of distilled water was added to each vial.

6. The vials were capped and bath-sonicated for five minutes to give crystal clear dispersions.

7. The plate from step (2) was washed in PBS/0.02% Tween 20 and then blocked by incubating for one hour with 1% BSA in PBS (300ul/well).

8. The plate was then washed as before, and 100ul of sample from each of the vials in step (6) was added to wells in column (1) of rows (1) to (7). Row (8) was left as a blank control.

9. Doubling dilutions were performed across the plate by transferring 100ul from wells in column (1) to the adjacent well on the same row in column (2) and mixing, then transferring 100ul to the next column as before, etc.

10. The plate was then incubated overnight at +4 degC.

11. The following day, the plate was washed as before and 100ul of commercial horseradish peroxidase-IgG conjugate (diluted 1/1000 in PBS) was added to each well and incubated at room temperature for 40 minutes.

12. The plate was then washed again, and 100ul of OPD substrate for peroxidase was added to each well and incubated at room temperature for 30 minutes.

13. 20ul of 3M sulphuric acid was then added to each well to stop the reaction.

14. The optical density of each of the wells was measured at 450nm on a plate reader, and the results obtained, after adjustment for background, are recorded below.

Sample		1 in 4	1 in 8	1 in 16	1 in 32	1 in 64
1	YFW	0.001	0.039	0.048	0.053	0.083
2	YFL	1.504	1.484	1.325	0.723	0.051
3	YWL	0.803	0.192	0.022	0.023	0.060
4	FWL	1.034	0.778	0.208	0.031	0.034
5	SEQ	0.029	0.041	0.055	0.057	0.091
6	SER	0.013	0.030	0.044	0.062	0.075
7	SQR	0.000	0.045	0.031	0.054	0.065

It can be seen that maximal binding is achieved with samples 2, 3 and 4 (ie combinations YFL, YWL, and FWL).

It can be seen that some, but not all, of the combinations of different headgroups enter into strong binding interactions, indicating that the response is specific to those particular combinations. The example illustrates the way in which the conjugates described can be employed in the combinatorial approach to identify efficacious combinations for the purpose of eliciting a desired binding interaction.

CLAIMS:

1. A composition for interacting with a ligand, which composition comprises a non-covalent association of a plurality of distinct conjugates, each conjugate comprising a head group and a tail group, wherein the tail groups of the conjugates form a hydrophobic aggregation and the conjugates are movable within the association so that, in the presence of a ligand, at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually.

2. A composition according to claim 1, wherein each conjugate has a head group selected from: an amino acid or peptide; a peptide analogue; a mono- or poly-saccharide; a mono- or poly-nucleotide; a sterol, a water-soluble vitamin; a porphyrin or haem nucleus; a metal ion chelate; a water-soluble drug; a hormone; and an enzyme substrate.

3. A composition according to claim 2, wherein each head group comprises an amino acid.

4. A composition according to claim 3, wherein each head group comprises a peptide comprising the amino acid.

5. A composition according to claim 3 or claim 4, wherein the head groups which form the epitope comprise terminal amino acids selected from at least two of the following:

hydrophobic amino acids, hydroxylic amino acids, acidic amino acids, amide amino acids, basic amino acids, and aromatic amino acids.

6. A composition according to any one of the preceding claims, wherein each tail group is the same or different and comprises a lipophilic group selected from a straight or branched-chain fatty acid, alcohol or aldehyde having at least 8 carbon atoms; a lipidic amino acid analogue; a prostaglandin; a leukotriene; a mono-or di-glyceride; a sterol; a sphingosine or ceramide derivative; and a silicon or halogen-substituted derivative of such a lipophilic group.

7. A composition according to claim 6, wherein each lipophilic group comprises a C_{10} to C_{14} fatty acid.

8. A composition according to any one of the preceding claims, wherein each conjugate further comprises a spacer group linking the head group to the tail group.

9. A composition according to claim 8, wherein the spacer group is hydrophilic.

10. A composition according to claim 8 or claim 9, wherein the spacer group comprises an amino acid, a hydroxy acid, a sugar or a polyethylene glycol.

11. A composition according to any one of the preceding claims, wherein the non-covalent association comprises a lamellar structure, a micelle or a liposome.

12. A composition according to any one of the preceding claims, for use as a medicament, a prophylactic or a diagnostic.

13. Use of a conjugate comprising a head group and a tail group, for the preparation of a composition according to any one of the preceding claims.

14. Use according to claim 13, wherein the head group is selected from: an amino acid or peptide, a peptide analogue; a mono- or poly-saccharide; a mono- or polynucleotide; a sterol, a water-soluble vitamin; a porphyrin or haem nucleus; a metal ion chelate; a water-soluble drug; a hormone; and an enzyme substrate.

15. Use according to claim 14, wherein the head group comprises an amino acid.

16. Use according to claim 15, wherein the head group comprises a peptide comprising the amino acid.

17. Use according to claim 15 or claim 16, wherein the amino acid comprises a terminal amino acid selected from hydrophilic amino acids, hydroxylic amino acids, acidic amino acids, amide amino acids, basic amino acids, and aromatic amino acids.

18. Use according to any one of claims 13 to 17, wherein the tail group comprises a lipophilic group selected from a straight or branched-chain fatty acid, alcohol or aldehyde

having at least 8 carbon atoms; a lipidic amino acid analogue; a prostaglandin; a leukotriene; a mono- or di-glyceride; a sterol; a sphingosine or ceramide derivative; and a silicon or halogen-substituted derivative of such a lipophilic group.

19. Use according to claim 18, wherein the lipophilic group comprises a C_{10} to C_{14} fatty acid.

20. Use according to any one of claims 13 to 19, wherein the conjugate further comprises a spacer group linking the head group to the tail group.

21. Use according to claim 20, wherein the spacer group is hydrophilic.

22. Use according to claim 21, wherein the spacer group comprises an amino acid, a hydroxy acid, a sugar or a polyethylene glycol.

23. A method for producing a composition for interacting with a ligand, which method comprises:

(a) providing a plurality of distinct conjugates, each conjugate comprising a head group and a tail group; and

(b) forming from the plurality of conjugates a non-covalent association thereof, in which the tail groups aggregate hydrophobically and in which the conjugates are movable so that, in the presence of a ligand, at least two of the head

groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually.

24. A method according to claim 23, wherein each conjugate is as defined in any one of claims 13 to 22.

25. A method according to claim 23 or claim 24, wherein the non-covalent association comprises a lamellar structure, a micelle or a liposome.

26. A method according to any one of claims 23 to 25, wherein the step of providing the plurality of conjugates comprises

(i) selecting a set of conjugates with an array of head groups;

(ii) forming a non-covalent association therefrom, in which the tail groups aggregate hydrophobically and in which the conjugates are movable;

(iii)assaying for sufficient interaction between the non-covalent association and the ligand;

(iv) optionally repeating steps (i) to (iii) using a set of conjugates with a modified array of head groups; and

(v) on finding sufficient interaction in step (iii) selecting the set of conjugates as the plurality of conjugates in step (a).

27. A method according to claim 26, wherein the array of head groups comprises (i) at least one terminal amino acid from each of the following classes of amino acid:

hydrophobic amino acids, hydroxylic amino acids, acidic amino acids and amide amino acids; and (ii) at least two further terminal amino acids comprising at least one basic amino acid and at least one aromatic amino acid, or at least two basic amino acids or aromatic amino acids.

28. A method according to claim 27, wherein the modified array of head groups used in step (iv) comprises the array of head groups used in steps (i) to (iii) in which the at least two further terminal amino acids are different from those used in steps (i) to (iii).

29. A method according to claim 26, wherein the array of head groups comprises (i) at least one terminal amino acid from each of the following classes of amino acid:
hydrophobic amino acids, hydroxylic amino acids, acidic amino acids, amide amino acids, basic amino acids and aromatic amino acids.

30. A method according to claim 29, wherein the modified array of head groups used in step (iv) comprises the array of head groups used in steps (i) to (iii) in which the at least

one terminal amino acid from one of the classes of amino acid is either absent or replaced by a charged version thereof.

31. A method for producing a molecule for interacting with a ligand, comprising:

(1) producing a composition according to the method of any one of claims 23 to 30;

(2) identifying the at least two head groups which form an epitope for the ligand in the composition; and

(3) producing a molecule incorporating the functional groups of the at least two head groups optionally spaced apart by one or more linker groups so that the molecule is capable of interacting with the ligand more strongly than each of the head groups individually.

Figure 1

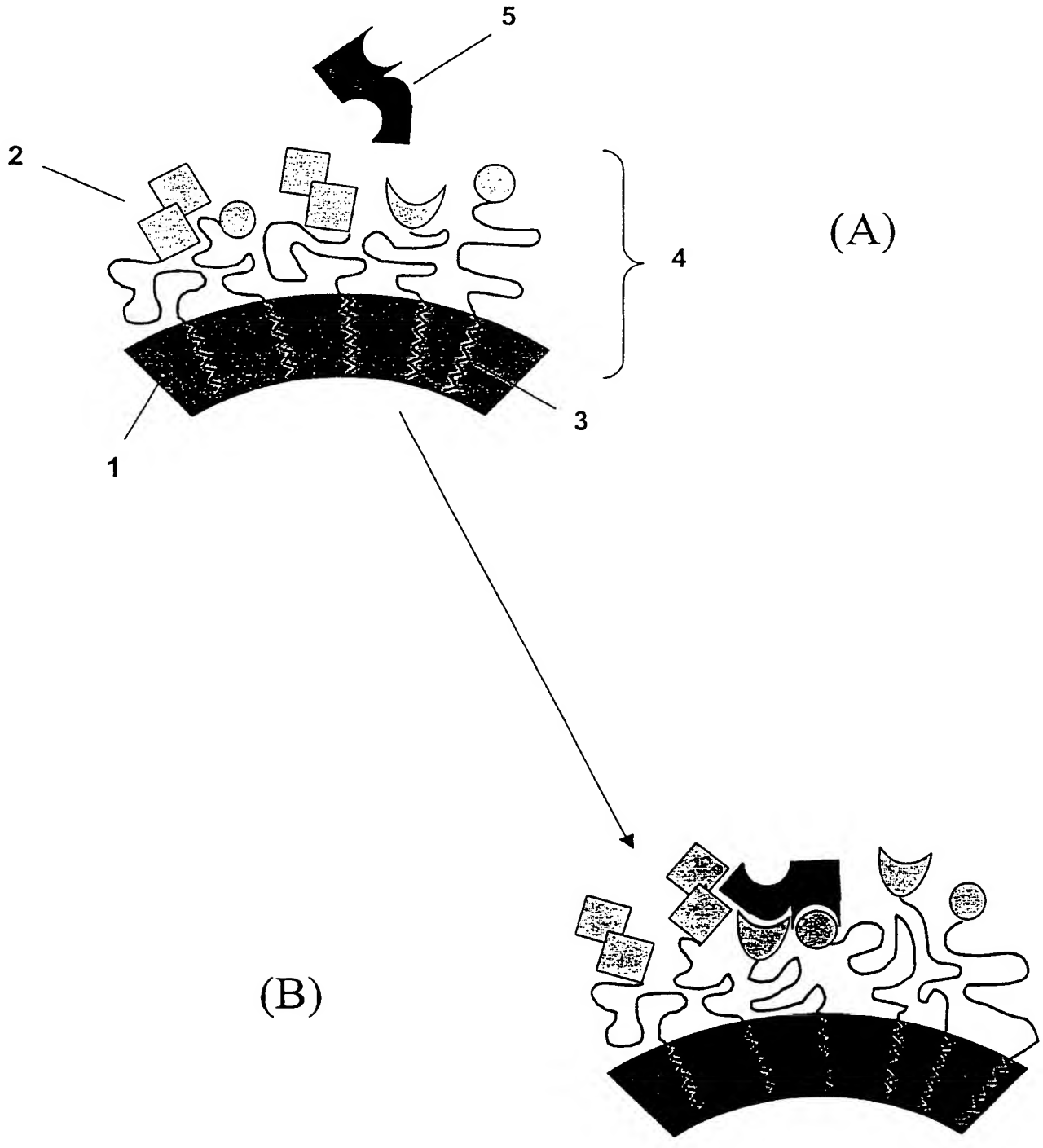
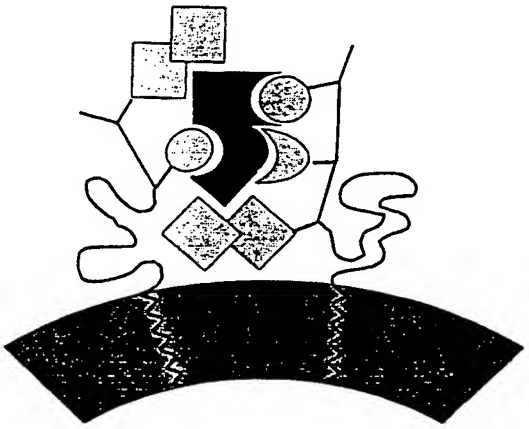
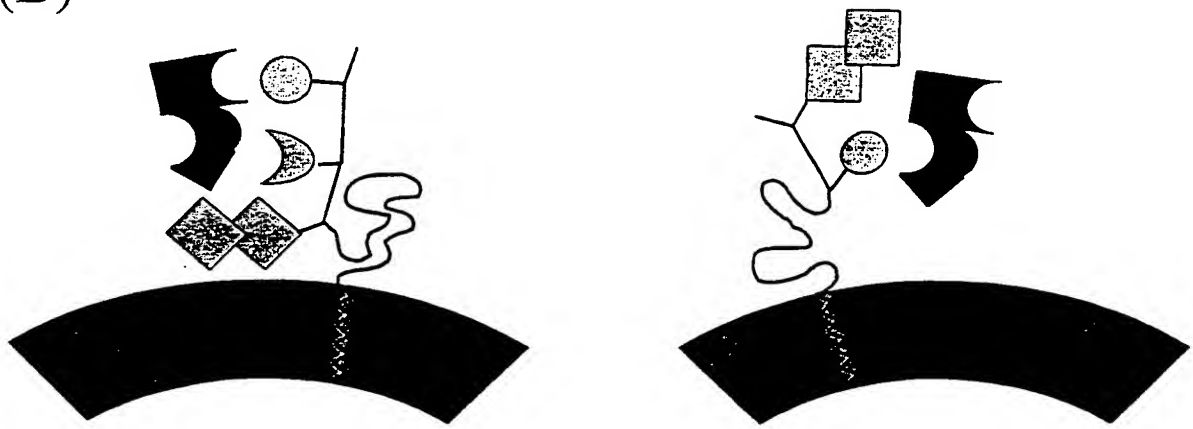


Figure 2

(A)



(B)



INTERNATIONAL SEARCH REPORT

Interna[illegible] Application No
PCT/GB 00/02465

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/543 G01N33/50 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 882 645 A (GIBBONS WILLIAM ANTHONY ET AL) 16 March 1999 (1999-03-16) figures 1-3	1-31
A	EP 0 338 437 A (HOECHST AG) 25 October 1989 (1989-10-25) page 5, line 48 - line 50; claims 1,7,8	1-31
A	US 5 580 563 A (TAM JAMES P) 3 December 1996 (1996-12-03) column 8 -column 9; figure 1; example 1	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2000	27/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hart-Davis, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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